degradation mediated by said proteasomes against other individual peptides remains unaltered.

REMARKS

The Examiner has objected to the Specification for specifically stated reasons. In addition, the Examiner has rejected the pending claims under 35 U.S.C. 112, first paragraph on a variety of issues; and under 35 U.S.C. 112, second paragraph as being indefinite in language. Finally, the Examiner has rejected the pending claims under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over either of U.S. Patent Nos. 5, 654, 273 or 5, 830, 993 respectively. In response, applicants have amended the Specification; submitted a new substitute Fig. 10; and amended claims 1-2, 6, and 11-15 respectively. By these amendments, figure submission and the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for objection and rejection stated by the Examiner in this second, non-final Official Action.

As a preliminary matter, applicants address the objection to the Specification made by the Examiner regarding the entry of SEQ ID NOS. for the description of Fig. 10 and the claims. While the grounds and authority for such objection are unstated, applicants have acquiesced to the Examiner's requests. Applicants have thus amended the Specification text at page 7, line 24 to include the proper SEQ ID NO. for Fig. 10; and also amended claims 12-14 to recite the appropriate SEQ ID NOS: in each instance.

Applicants respectfully question the Examiner's demand for the inclusion of such formal details. Nevertheless, to avoid senseless argument, applicants have acquiesced to the Examiner's explicit demands on this issue. For these reasons, applicants therefore request that the Examiner reconsider her stated position and withdraw these grounds of objection pending application.

Applicants will now address each substantive basis for rejection stated by the Examiner in the instant Official Action with respect both to the legal requirements and the relevant factual circumstances. However, because so much of the Examiner's stated views and positions are dependent upon a proper recognition of applicants' invention as defined by the language of the presently pending claims, applicants deem it both useful and necessary to summarily review the scope and delineation of the subject matter as a whole which is applicants' claimed invention.

I. Applicants' Invention

Applicants' invention is defined in the alternative by claims 1-10 and by claims 11-15. Claims 1-10 define a methodology while claims 11-15 are composition of matter definitions directed to a family of pharmacologically active oligopeptides for use in the recited methodology.

A. The Method Claims

It will be recognized and appreciated that amended independent claim 1 is directed to a method for stimulating angiogenesis within a targeted collection of viable cells in-situ;

whereas amended independent claim 2 defines a method for altering proteasome-mediated degradation of peptides in-situ within a collection of viable cells. As stated, independent method claims 1 and 2 are similar in the limitations and requirements recited by their manipulative steps. Each method claim identifies a collection of cells in-situ as the target; provides means for introducing at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of the targeted cells; introduces at least one member of the PR-39 oligopeptide collective to the targeted cells; and then explicitly requires that the introduced PR-39 oligopeptide collective member interact with such proteasomes as are present within the cytoplasm of the targeted cells in three specified ways.

These three requisite interactions are: that the $\alpha 7$ subunit of the proteasomes interact with the introduced PR-39 oligopeptide collective member; that the proteolytic degradation mediated by these proteasomes with an interacting $\alpha 7$ subunit against an identifiable peptide becomes markedly inhibited while the proteolytic degradation against other individual peptides remains unaltered; and that the markedly inhibited proteolytic degradation activity of these proteasomes with an interacting $\alpha 7$ subunit results in a stimulation of angiogenesis in-situ as recited by claim 1 or results in an increased expression of an identifiable peptide (such as IK$\beta\alpha$ or HIF- 1α) as recited by claim 2.

B. The Methods Claims Recite An Explicitly Required Mechanism of Action

The Examiner will also recognize and appreciate that the three requisite interactions demanded by claims 1 and 2 respectively explicitly recite a precise mechanism of action; and also demand that both the resulting stimulation of angiogenesis in-situ (claim 1) and the increased expression of an identifiable peptide in-situ (claim 2) be the direct consequence and

outcome of the interactions between the introduced PR-39 oligopeptide collective member and the α7 subunit of the proteasomes within the targeted cells. Applicants respectfully submit and maintain therefore that the Examiner cannot separate or divorce the recited manipulative steps and the required α7 subunit proteasome interactions with the PR-39 oligopeptide collective member from the consequential and resulting cellular outcomes. Thus, the human interventional act of introducing a PR-39 oligopeptide collective member to the targeted collection of cells is the explicitly causative act; while the PR-39 oligopeptide interactions with the α7 subunit of the proteasomes is the explicitly required means and mechanism; and the stimulation of angiogenesis and/or the increased expression of an identifiable peptide is the explicit consequential result and intended outcome of the recited human acts of intervention.

C. Applicants' Defined Methodology Is A Statement of Overt Human Intervention

The Examiner will recognize and appreciate also that applicants' invention, as defined by amended claims 1-10 individually, comprises acts of human intervention which are presented in the form of a method claim having a series of explicitly stated manipulative steps. Method claims are acts of overt human intervention and are recitations of human manipulations which may employ a machine, article of manufacture, or composition of matter as a workpiece. This form of claiming applies to a newly recognized use or application for any composition of matter , even one which is previously known. Accordingly, the essential question for the Examiner is whether the recited acts of human intervention - defined as a series of manipulative steps - constitute a procedure which is operative, novel and non-obvious to a person of ordinary skill in the field of the invention.

It is especially important, when evaluating the patentable merit of applicants' defined method claims to remember that it is not pertinent whether the compositions of matter employed (the PR-39 oligopeptide collective member) in the recited procedure are themselves known, or are entirely new, or are themselves unobvious. The relevant issue is, rather, whether the recited manipulative steps recited by the method claims have patentable merit in light of the teachings in the prior art references given the perspective of the ordinary practitioner in that field [In re May, 197 U.S.P.Q. 601 (C.C.P.A. 1978)].

II. The Examiner's Underlying Erroneous Views

Applicants and their undersigned attorney find the Examiner's stated views and positions concerning the definition of the present invention to be both factually inaccurate and legally erroneous with regard to applicants' invention as disclosed by the description of the Specification text and the law established by the controlling caselaw decisions. Throughout the entirety of the instant Official Action [as well as the prior first Official Action], the Examiner has overtly refused either to recognize or accept any and all information or evidence that the manipulative steps recited by the method of claims 1 and 2 constitute external acts of human intervention, or could be anything other than "**an inherent event**". This subjective belief pervades the entirety of the Examiner's evaluation and review, regardless of the specific issue or rejection basis under consideration; and has so deeply tainted the perspective and objectivity of the Examiner's state of mind that is has become impossible for the Examiner either to assess critically the facts or to render an objective positional statement regarding the true facts and merits of the present invention.

The Examiner's erroneous belief is stated openly only at pages 7-8 of the instant Official Action; but is employed as the given reason for rejection concerning novelty and non-obviousness as stated at page 5, top as well as at page 6, top of this Official Action. However, the Examiner's erroneous and unsupported view is tacitly presented and in effect throughout each and every basis of rejection stated by the Examiner within the whole of the instant Official Action. The Examiner's subjective position, as explicitly presented in the instant Official Action, states:

". . . Clearly, if the peptide of the prior art would bring about the results, i.e., 'stimulation of angiogenesis', it inherently follows the specified and postulated mechanism steps. Even assuming arguendo that the prior art failed to disclose or suggest a 'latent' or 'inherent' property, the caselaw recognizes time and again the 'mere recognition of latent properties in the prior art does not render non-obvious an otherwise known invention' . . ." [Page 7, lines 1-15 of the instant Official Action]/

". . . Because proteasomes are an integral part of the cytoplasm and are expected to inherently perform their function, as explained by the applicant . . ." [Page 8, lines 8-9 of the instant Official Action"].

"Remarks regarding the rejection of the claims 1-10 under 35 U.S.C. 102(b)/103(a) over Gallo et al., are not convincing. The reference teaches that: a) PR-39 is known in the and b) PR-39 is useful in treating angiogenesis (abstract). The be effective in treating angiogenesis it must inherently follow a mechanism for its action . . ." [Page 8, lines 10-13 of the instant Official Action].

In an attempt to justify these views and positions, the Examiner has acted subjectively, erroneously and prejudicially. The Examiner has chosen to ignore the entire body of evidence, information and facts disclosed by the Specification text; and the Examiner has repeatedly refused either to recognize or to admit the clear meaning of the acts of human intervention and the mechanism and consequential effects of the overt human manipulations recited by the steps of independent claims 1-2; and the Examiner has chosen to evade from the controlling effect and legal authority of the long-established caselaw decisions that

properly and lawfully deny and refute the Examiner's reasons for these explicitly stated views regarding inherency. Ample evidence demonstrating all of these prejudicial errors is presented below.

A. The Antecedent Description Basis Properly Supports the Claims

Applicants' respectfully direct the Examiner's attention to Specification text in order to demonstrate the presence of an ample and complete description for each and every manipulative step of the methodology defined by amended independent claims 1 and 2 respectively herein. The underlining mechanism for the methodology is described beginning at page 9, line 17, and continues through page 11, line 15. As repeatedly disclosed therein, one essential requirement is the presence of a proteasome and at least one member of the collective of PR-39 oligopeptides. Also, the detailed description for the mechanism of interaction for proteasomes and selective polypeptide degradation function is described in detail particularly beginning at page 10, line 5 and continuing through page 11, line 1.

In addition, the membership of the PR-39 oligopeptide collective is also described in precise, clear, and explicitly complete detail within the Specification beginning at page 22, line 4 and continues through page 26, line 7. Attention is directed to the Specification text at page 24, lines 18-22 in particular – especially with regard to the information presented at pages 25-26.

B. The Nature Of The Examiner's Erroneous Reliance On The Legal Doctrine Of Inherency

The Examiner has acknowledged that the individual cited and applied references do not explicitly or directly disclose those particular attributes, properties and capabilities of the method defined by claims 1-10. Instead, the entirety of the Examiner's reasoning is based on the legal doctrine of inherency. The Examiner's remarks and conclusions (as stated at pages 7-8) also state that the mechanism of action recited by the claims under review is not relevant or material to the issue; and that all the peptides described within the Specification text per force inherently possess the characteristics recited in the instant claims –"if the peptide of the prior art would bring about the results, i.e., 'stimulation of angiogenesis'."

The Examiner, (as shown by her remarks within the instant Official Action) has knowingly confused and confounded the "inherency" legal principle by intentionally and erroneously: (a) ignoring the legal requirement that the stated goals and objectives of the presently claimed method must be substantially similar or identical to those purposes disclosed in the prior art references; (b) denying the long-recognized and legally-required linkage that the observed "result" is not the correct measure of inherency, but that a specific mechanism of action must be involved and specified operative interactions must be the true cause and initiator causing or creating the observed outcome and result; and (c) basing the entirety of a rejection on the legal doctrine of inherency without any true factual support or evidentiary basis other than a personal and subjective belief upon an existence of allegedly "latent" biochemical properties or "unrecognized interaction" – all of which are factually unknown in the prior art and all of which have no evidentiary or empirical underpinnings.

Furthermore, the Examiner has not employed the "doctrine of inherency" as established in law by the controlling caselaw decisions; but instead has created her own personal subjective and artificially contrived "latency" doctrine - which is an oversimplified, fragmented and distorted overgeneralization of the legally correct 'inherency doctrine'. The Examiner's overt attempt to create and impose an arbitrary and self-created legal standard is clearly prejudicial and improper.

C. The Proper Legal Requirements And True Limits Of The 'Inherency Doctrine'.

Applicants respectfully submit and maintain that the entire substance of the Examiner's presentation, rationale, and position is centered on an erroneous and distorted interpretation of the legal doctrine of inherency. Accordingly, a proper presentation and clear understanding of the legal doctrine of "inherency" is presented here.

The legal doctrine of "inherency" holds that anticipation and also obviousness may be established when a prior art reference either discloses exactly or suggests overtly the identical goals of a claimed invention; and also provides both the materials and the manner of use for the materials which will then yield the intended goal as the consequential result.

Unfortunately, the Examiner has failed to recall that the legal doctrine of inherency is available only when the claimed invention can be identified or inferred from the disclosure within the prior art reference with substantial certainty. Probabilities and speculation are not a substitute for substantial certainty; and probabilities and speculation are not legally sufficient to invoke and apply the inherency doctrine [In re Oelrich, 212 U.S.P.Q. 323 (C.C.P.A. 1981); In re Chandler, 117 U.S.P.Q. 361 (C.C.P.A. 1985)].

In order for a claimed invention, such as a method, to be inherently disclosed, all the requirements recited by the steps of the method as claimed must be the necessary and only reasonable construction to be given to the prior art disclosures; and the resultant method as claimed in its entirety must inevitably occur and be the result of what is revealed in the prior art. Moreover, the mere possibility that a certain result may or might result from the factual circumstances is not legally sufficient to establish inherency [In re Robertson, 49 U.S.P.Q. 2d 1949 (Fed Cir. 1999)]. The legal obligation and the evidentiary burden thus lies solely upon the Examiner to demonstrate not only that any of the cited and applied prior art references might provide the result, consequence, property, or trait with substantial certainty; but also to demonstrate that the manner and mechanism of activity exists and is operative to provide the intended result. If, however, the consequence or result could only potentially or speculatively occur as a theoretical possibility or contingent event within the factual setting; or when there is no factual basis operative or sequence of manipulations known for effecting for effecting the desired outcome, then this basis is inadequate legally and insufficient [Continental Can Co., U.S.A. Inc. v. Monsanta Co., 20 U.S.P. Q. 2d 1746 (Fed. Cir. 1991)].

It is therefore well established, as a matter of law, that for an event, outcome or result to be deemed as inherently disclosed or suggested, it is not sufficient that the ordinary person following the prior art disclosure(s) might – by some unknown procedure, process or mechanism – obtain the desired result. To the contrary, it is legally demanded that an identifiable mechanism and means operative to produce the outcome or result be knowingly in force. Inherency as a doctrine and the legal basis for rejection cannot be proven or established upon a personal speculation or where reasonable objective doubt exists as to whether or not the intended results occurs [In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976)].

With all these points in mind, applicants and their undersigned attorney will now address each of the individual bases of rejection presented by the Examiner in the instant Official Action.

III. The Rejection Under 35 U.S.C. 112, first paragraph

The Examiner has rejected the previously pending claims under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the Specification. The essence of the Examiner's view is that certain newly added wording to the pending claims broadens the scope of the claims beyond what is described by the disclosure of the Specification text. In specified instances (such as the word 'functionally'), the Examiner views the new language as being New Matter (page 3, middle); in other specified instances, the Examiner finds the original claim language to lack description (page 2, bottom), or to be speculative (page 4, top), or even not to be credible regarding utility. Unfortunately, the Examiner is in error in each of these instances.

A. The Legal Requirement For Adequacy Of Description

A fairly uniform standard presently exists for determining if the written description requirement of 35 U.S.C. 112, first paragraph has been sufficiently complied with and satisfied by the disclosure of a Specification in a pending application. The caselaw decisions and legal analyses to date state that the test for legal sufficiency of descriptive support in a Specification's disclosure is whether or not the disclosure of the pending application

reasonably conveys to the person of ordinary skill in that art that the inventor has possession of the innovative subject matter as then defined by the pending claims. Thus to be legally sufficient, the written description must clearly allow persons of ordinary skill in the art to recognize that, after reading the Specification test, applicant invented that which is claimed [In re Gosteli, 10 U.S.P.Q. 2d 1614 (Fed. Cir. 1989); In re Kaslow, 217 U.S. P.Q. 1089 (Fed. Cir. 1983)].

For this inquiry, fact specificity is central and essential to the issue. When evaluating and deciding the adequacy of written description, the primary consideration in each instance for the Examiner is the quality and quantity of factual detail provided by the disclosure – which in turn, must and will depend upon and vary with the nature of the subject matter which is the invention as well as determine the amount of information and knowledge properly needed to be imparted to those of ordinary skill in the art by the Specification text [In re Wertheim, 169 U.S.P.Q. 795 (C.C.P.A. 1971); Vas-Cath Inc., v. Makurkar, 19 U.S.P.Q. 2d 1111 (Fed. Cir. 1991) and the citations listed therein at p. 1116].

These caselaw decisions routinely point out and stress that the written description requirement of Section 112 is an issue which must be decided on its own facts in each instance with due regard for the nature of the specific invention, the scope of the claims as written, and the state of pertinent knowledge then existing in that art or technical field. Overall therefore, legal compliance requires merely that the written description when reviewed in its entirety provide and place in the reader that knowledge and information constituting what applicant considers and claims as his own invention in such degree that the invention as disclosed and claimed can be understood in full and clearly distinguished from that which is already known or in common use [In re Smith and Hubin, 178 U.S.P.Q. 620

(C.C.P.A. 1973); In re Wright, 9 U.S.P.Q. 2d 1649 (Fed. Cir. 1989); Ralston Purina Co. V. Far-Mar-Co. Inc. 227 U.S.P.Q. 177 (Fed. Cir. 1985); Vas-Cath Inc. v. Makurkar, 19 U.S.P.Q. 2d 1111 (Fed. Cir. 1991)].

B. The Examiner's Legal Obligation

Applicants believe it is useful also to provide a summary of the pertinent caselaw and the underlying legal requirements regarding a rejection based on a non-descriptive specification. As a matter of established black letter law, the Examiner is legally required and obligated to present sufficient facts, reasoning, and evidence from which to doubt the objective truth of the information disclosed by the Specification; and also to explain why the Examiner doubts the truth, accuracy or sufficiency of any statement in the Specification [In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971)].

The Examiner must also back up his assertions with acceptable evidence or reasoning which is inconsistent with the information or statements disclosed by the Specification. Thus it is incumbent on the Examiner first to establish a prima facie case; and, second, to provide a factual basis to support the rejection, rather than making a merely conclusionary statement that the practice of the invention would be beyond the skill of the practitioner in this art [In re Bredner, 173 U.S.P.Q. 169 (C.C.P.A. 1972); In re Armbruster, 185 U.S.P.Q. 152 (C.C.P.A. 1975)]/

Also, because the Examiner bases her rejection in terms of the claims being of undue scope or containing new matter, the relevant legal inquiry therefore is whether the disclosure

provided by the Specification is commensurate in scope with the protection sought by the language of the pending claims [In re Cescon, 177 U.S.P.Q. 264 (C.C.P.A. 1973)]. This requirement is satisfied and fulfilled when one possessed of the knowledge disclosed by the Specification could then use the invention given the disclosure of the Specification [In re Eynde, 178 U.S.P.Q. 470 (C.C.P.A. 1973)].

With these legal standards in mind, applicants respectfully submit that the Examiner has failed to provide the requisite underlying factual basis which demonstrates an absence of sufficient information or description within the Specification text.

C. The Examiner's Stated Reasons For the Rejection

As stated, the Examiner has specifically focused her remarks [page 3, middle of the instant Official Action] on the words "functionally" and "selectively" as well as the meaning of these words within the manipulative steps recited by the originally submitted claims. Applicants respectfully submit that the Examiner is acting subjectively and is indulging merely in semantic gamesmanship.

It is clear from the description provided by the Specification text itself that the original term "selectively" refers to and defines the empirically demonstrated fact that the $\alpha 7$ subunit of proteasomes, after interaction with any member of the PR-39 oligopeptide collective, becomes markedly altered in its proteolytic degradation capacity such that specific degradation of individual peptides such as HIF- 1α and $I K \beta \alpha$ is reduced - but without altering the proteolytic degradation of other individual peptides such as page 105 and page 50 NFKB.

Thus, the plain meaning of the words "selectively", "functionally" is, was and remains fully disclosed and amply described by the Specification text.

Consequently, with respect to the Examiner's stated view and position on this matter, applicants respectfully submit that there is no information or description content which is lacking from the written disclosure of the Specification text which could meaningfully effect or influence the meaning of the terms "selectively" or "functionally". Yet, the Examiner has chosen to question the descriptive adequacy of these words and has rejected the claims as being either "New Matter" or vague.

The sole rationale explanation for the Examiner's stance, in so far as applicants can understand, has been a continuing subjective reluctance and personal opposition to the word "selectivity" as employed within the language of the original claims defining the methodology; or to any other words of similar meaning as recognized and used in conventional connotative English (such as "functionally"). Applicants note that the doctrine of *"In hac verbis"* has long been formally disavowed, legally dismissed, and abandoned as a policy and practice by the U.S. Patent Office; and, as an integral part of this reform policy, is the now well-established practice to avoid any legal requirement or overt need to include or present formal language definitions or recitations of meanings for commonly used words – especially when the text and description of the Specification makes the proper meaning and operational definition of the word or phrase abundantly clear and well understood in context as written.

As for the other points raised by the Examiner, these are purely unsubstantiated, personal remarks that have no underlying fact basis or legal support. The terminology of claim 5 regarding "reception-specific peptide means" and "slow-releasing means" is language

which represents conventional and commonly used terms in the relevant technical field. The Examiner, however, has not deemed it necessary to proved even an explanation to support her personal view.

Similarly, regarding the language of claim 6, the Examiner chooses to provide the readers with her subjective and speculative theories about the potential future of "gene therapy"; and tacitly demands empirical proofs for the intracellular expression of DNA sequence coding without any valid reasons or factual basis.

A third instance of the Examiner's subjective and unsupported belief is her refusal to credit any "utility" for claim 2 as well as her insistence that the operability of claim 2 is not considered credible. This view is presented, however, without benefit of facts, evidence, or even a rational explanation.

Applicants have neither need nor desire to argue semantics or personal quirks with the Examiner. It is, however, applicants' purpose and intent to advance the prosecution of this application on substantive grounds; and applicants have acted on their intent herein.

Thus, solely in order to resolve such questions in an expeditious manner, applicants have chosen to amend the language of the methods defined by independent claims 1 and 2 by including a recitation of what the original term "selectively" encompasses, as disclosed in detail within the Specification text itself. In this manner, the Examiner's stated view and position has been directly and effectively addressed; yet, the true meaning of the terminology and language as described within the Specification text and recited within the manipulative steps of the method is explicitly set forth and is commensurate in scope with the antecedent descriptive for the invention as a whole. Such amendment is believed to be proper and correct in all aspects.

Overall therefore, applicants have substantively amended claims 1-2, 6, and 11-15. The alleged flaws in wording identified by the Examiner have been addressed in these claims; and the claim language has been amended, conforming precisely to the description of the Specification in order to meet the Examiner's stated basis for rejection. The amended language of all these claims is therefore believed to be correct and satisfactory in all respects with regard to the requirements of the first paragraph of 35 U.S.C. 112. Accordingly, Applicants request that the Examiner reconsider her stated position and withdraw this ground of rejection against the presently pending amended claims.

III. The Rejection Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected original claims 1-10 as being indefinite for failing to particularly point our and distinctly claim the subject matter which applicants regard as their invention. The problem again appears to be centered on the use of the words "functionally", "discriminating", and even "substantially" in the claim language.

With all due respect to the Examiner, her stated reasons as given are merely additional instances of the Examiner's refusal to recognize or accept common synonyms and equivalent terminology for particular words or phrases in the original claims. The Examiner is once again indulging in extreme semantic gamesmanship; and is again presenting a subjective viewpoint which is personal and prejudiced with regard to the definiteness of certain words. Merely illustrating one example of the Examiner's semantic extremism is her belief that the word "substantially" is legally indefinite – all in spite of the fact that this word

"substantially: has been upheld repeatedly in reported caselaw decisions as being both legally sufficient and proper for use in claim language as regards the 2nd paragraph of Section 112.

Finally, as regards the language of the presently pending claims as a whole, the first inquiry is to determine whether the claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular use or application disclosed by the Specification as it is understood and interpreted by one possessing ordinary skill in the pertinent art [In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976)]. Applicants note that each of the terms used in the pending claims is well understood; it not subject to numerous definitions and interpretations; and that there is no discrepancy, no confusion, and no ambiguity with regard to the antecedent descriptive basis provided by the Specification text. Rather, the language of the claims as a whole now pending read on subject matter which is completely described and enabling by the Specification text. Moreover, each of the pending claims is explicit and clearly stated, and sets forth and circumscribes the particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularity required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiner reconsider her stated position and withdraw this ground of rejection against the presently pending claims.

IV. The Rejection Under 35 U.S.C. 102(b) and 103(a)

The Examiner has rejected claims 1-15 under 35 U.S.C. 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being obvious over either the Gallo et al. reference [U.S. Patent No. 5, 654, 273] or the Blecha et al reference [U. S. Patent No. 5,830,993]. The Examiner states that each cited and applied patent reference inherently discloses a method for treating angiogenesis using known PR-39 compositions. The Examiner also states that because the claims in the present application are drawn to a method of using a known peptide for treating a condition taught by the art – without regard to the mechanism of action employed and in effect – applicants' methodology is deemed to be 'inherently anticipated' and/or 'rendered obvious' by the prior art.

Applicants have respectfully pointed out and showed herein that the Examiner is legally in error as regards her use of the inherency doctrine with regard to the issues of novelty and non-obviousness. Applicants submit and affirm that the Examiner's position and presumption as regards these issues is a fallacy; and that the Examiner's reliance upon the inherency doctrine is based solely upon a speculative therapy which has no factual basis to support it. Applicants also respectfully maintain that the Examiner has not presented or established any evidence with the requisite degree of substantial certainty which proves any inherent property with regard to angiogenesis stimulation capabilities or the altered proteasome degradation properties of the methods now recited by amended claims 1-10 or the oligopeptide compositions now defined be amended claims 11-15 herein.

Moreover, the Examiner's continuing reliance and use of the inherency doctrine fails to meet minimal legal requirements and may not be properly employed as a legal basis for

rejection - because the body of evidence employed by the Examiner as the underline basis for rejection is purely speculative, and can only be characterized as a self-serving theory without any realistic probability as such. This is demonstrated factually by the absence of relevant supporting information, knowledge, or data with either of the two cited and applied patents, as is demonstrated hereinafter.

Under these circumstances, however, a summary review of the requisite legal standards concerning anticipation and non-obvious is first in order.

A. The Proper Legal Standards For Determining Novelty And Non-Obviousness

As a matter of long established law, anticipation under 35 U.S.C. 102(b) requires exact identity of the claimed process or claimed composition within a conventionally known method or procedure existing previously in the prior art. The claimed composition or the claimed process, including each manipulative step defining the methodology as a while, must be described or embodied, directly or indirectly, within a single reference. Anticipation thus requires exact identity or effective duplication of applicant's claimed invention; and the single reference of record must describe applicant's claimed invention sufficiently in detail such that a person of ordinary skill in that field has possession of the invention itself. Also, in deciding the issue of anticipation, the Examiner must identify each requisite element as recited within the claims; determine their meaning in light of the Specification; and identify the existence and presence for each of the corresponding elements as being disclosed in the allegedly anticipating reference [Scripts Clinical and Research Foundation vs. Genentech Inc., 18

U.S.P.Q. 2d 1001 (Fed. Cir. 1991); Glaverbel Society Anonyme vs. Northlake Marketing and Supply Inc., 35 U.S.P.Q. 2d 1496 (Fed. Cir. 1995)].

It is useful here also to identify the legal basis and standard for obviousness under 35 U.S.C. 103. Where applicant's claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: 1) whether the prior art of record would have suggested to those of ordinary skill in the art that they should carry out the claimed process or make the claimed composition; and 2) whether the prior art would also have revealed that in so carrying out or making, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988)]. Both the suggestion and the reasonable expectation of success must be found within the prior art references(s) themselves and not in applicant's disclosure [In re Vaeck, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991)]. In addition, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art might be modified in the manner suggested by an Examiner does not make that modification obvious unless the prior art suggested the desirability of the modification [In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicants therefore respectively affirms and submits that the Examiner's stated views and conclusions in the instant Official Action have failed to conform to the legal standard and requirements for anticipation as well as for obviousness. A summary review of the substantive content within each cited and applied patent reference will reveal the errors in the Examiner's stated positions.

B. The Content of the Cited And Applied References of Record

Applicants and their undersigned attorney will now review each of the two prior art references of record individually and in detail. These are (a) the Gallo et al. patent, No. 5,654,273; and (b) the Belcha et al. patent, No. 5,830,993.

In conducting the review of the facts disclosed within each of these prior art references, applicants will take special care to point out what the goals and objectives for each referenced invention are as explicitly stated within the reference; the means and manner in which each referenced invention is said to be functional and operative; and, the explicitly recognized limitations and restrictions of each invention as stated by the reference itself. The Examiner's attention is directed particularly to these points of information as the best evidence and proof of the Examiner's repeated errors.

The Gallo et al. '273 patent

1. The Gallo *et al.* invention is explicitly directed to wound repair using a peptide inducer of syndecan expression which is effective only in particular cells [Column 1, lines 10-12; Column 2, lines 13-19]. The syndecans able to be induced in particular kinds of cells are syndecan-1 and syndecan-4 [Column 2, lines 27-30; Column 3, lines 16-18].

2. As disclosed, the composition of matter able to induce syndecan-1 and syndecan-4 expression in particular cells types is a 39 amino acid peptide termed "PR-39" and its biological active derivatives – which (a) have the same or functionally equivalent changed in structure, and, (b) include the amino acid sequences Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-

Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid [Column 3, lines 26-34]. This syndecan-inducing composition of matter could also be part of a fusion protein, or be immobilized to an inert substrate, or be targeted using a specific ligand, or be a part of a longer protein [Column 3, lines 35-39].

3. The disclosed composition of matter comprising the PR-39 required amino acid residue sequence are collectively identified as "syndecins". All such syndecins collectively must demonstrate specific biological activities which include: (a) the specific inducement of syndecon-1 and syndecon-4 expression on the surface of mesenchymal cells; (b) the specific inducement of syndecon-1 and syndecon-4 mRNA within mesenchymal cells; (c) an increase in the level of mesenchymal cell surface heparin sulfate; and (d) a rapid uptake into mesenchymal cells to a saturation level [Column 3, lines 39-46].

4. The PR-39 peptide composition as disclosed was identified, isolated from and found to be an active agent for inducing syndecan-1 expression as a component of wound fluid. Example 1 in the reference describes the experiment in detail [Column 6, lines 20-67; Column 7, lines 1-16]. Similarly, the degree of syndecan induction was experimentally shown to vary directly with the concentration of PR-39 in wound fluid as described by Example 2 [Column 7, lines 20-67; Column 8, lines 1-23]. In this manner, the relationship between PR-39 in wound fluids and the induced expression of syndecon-1 and syndecon-4 in mesenchymal cells was empirically demonstrated and proven.

5. The selectivity of wound fluid and of PR-39 induction capability is then demonstrated as being overtly controlled by particular cell type. As disclosed explicitly by Example 4, all the non-mesenchymal cell types tested (4 major types) failed to respond to the effects of PR-39 in the wound fluid [Column 8, lines 51-65]. Only the mesenchymal cell varieties selectively responded to the inducing effects of PR-39 in the wound fluid; and only the mesenchymal cell types selectively showed the biochemical changes demonstrative of syndecan-1 induction [Column 8, lines 66-67; Column 9, lines 1-10].

6. The explicitly stated uses and intended application for PR-39 peptide compositions is for wound repair via the induction of increased syndecan-1 and syndecan-4 mRNA levels [Column 2, lines 23-39]. Only in this manner will the PR-39 peptides function in promoting wound healing as well as treating other disorders involving mesenchymal cells and ligand interactions with cell surface heparan sulfate [Column 2, lines 40-43]. These limited clinical applications and the explicitly stated demand and requirement which relies on the increased expression of syndecan-1 and syndecan-4 on the surface of mesenchymal cells using PR-39 peptides as the explicit means and manner by which the wound healing result is obtained – is set forth in detail within the reference itself [Column 5, lines 1-67; Column 6, lines 1-17].

In sum, therefore, the following factual limits and requirements are explicitly taught by the disclosure of the Gallo et al. '273 patent reference: (a) The PR-39 peptide is disclosed, empirically tested and presented as a peptide useful only for induction and expression of syndecan-1 and syndecan-4 on the surface of mesenchymal cells and is functional for the explicit purpose of increasing mesenchymal cell surface heparan sulfate. (b) The PR-39

peptide is very selective as to particular cell type and is biochemically active as a "syndecin" only with cells of mesenchymal origin. The PR-39 peptide and its derivatives collectively are inactive with all cell types which are non-mesenchymal cells, especially cells of cerebral origin and epithelial origin. (c) The means and manner by which the PR-39 peptide exerts its biochemical effects is solely via the induction of cell surface syndecans and is limited to the consequential increase of cell surface heparan sulfate in cells of mesenchymal cell origin as the intended result. (d) The explicitly stated value and intended function of the PR-39 peptides is as a healing agent for use with wounds and in clinical disorders which involve mesenchymal cells and ligand interactions with cell surface heparan sulfate. This explicitly stated mechanism of action and intended outcome is required in each and every clinical application disclosed without exception.

The Blecha *et al.* '993 patent

1. The Blecha *et al.* invention is explicitly directed to the synthesis of anti-microbial peptides which can be used for inhibiting microbial growth and microbial infections [Column 1, lines 3-33]. The synthesized anti-microbial peptides are compositions based on the 39 amino acid residue sequence of PR-39 peptide isolated from wound fluid and shown previously to be able to induce syndecan expression on mesenchymal cells [Column 1, lines 33-55].

2. The Blecha *et al.* anti-microbial peptides are analog compounds based upon the known structure of PR-39 peptide, but are truncated peptides which still retain the functional anti-microbial domain of the original PR-39 peptide structure [Column 1, lines 61-65]. All of these truncated peptides, however, must retain the demonstrated anti-microbial property of the

original PR-39 peptide – that is, the active killing of microorganisms or the active suppression of microbial multiplication and/or growth [Column 1, lines 61-67; Column 2, lines 1-3].

3. The Blecha *et al.* disclosure sets forth a series of in-vitro assays by which to determine empirically which of the synthesized, truncated peptide compounds derived from the original PR-39 structure possess the requisite anti-microbial activity. These assays include: the gel-overlay assay, the lawn-spotting assay, the minimal inhibitory concentration test, the measurement of post antibiotic effects, the susceptibility of neutrophil phagocytosis, the regulation of neutrophil superoxide anion production, neurophil chemotaxis capability, and the influence on intestinal epithelial cells [Column 3, lines 33-67; Column 4, lines 1-67; Column 5, lines 1-46].

4. The Blecha *et al.* reference discloses that six truncated analog peptide structures based on the original PR-39 peptide were synthesized as is shown by Fig. 1 of the patent. Of these, only three truncated peptide analogs had an amino acid residue sequence which began using the N-terminal end of PR-39, but exist as shorter length peptide structures. These three truncated analog structures are the PR-14, PR-19 and PR-26 peptides. In comparison, the truncated PR-15 peptide structure contained only a portion of the COOH-terminal residues of the original PR-39 peptide sequence; and the truncated PR-16 analog contained only residue Nos. 11-26 in the original PR-39 structure; and the truncated PR-23 analog contained only residue Nos. 4-26 of the original PR-39 peptide sequence. Thus, none of the PR-15, PR-16 or PR-23 truncated peptide analog structures contained an N-terminus sequence beginning with the amino acid resides Arg-Arg-Arg [Column 5, lines 47-67; Column 6, lines 1-27].

5. The Blecha *et al.* disclosure also states that of the six truncated analog peptide structures synthesized and tested, only the truncated PR-26 analog structure was found to have any anti-microbial activity in comparison to that of the original PR-39 peptide [Column 6, lines 29-47]. The empirical data presented revealed that only the PR-26 truncated peptide analog demonstrated the required anti-microbial killing properties using the in-vitro assays [Column 6, lines 59-67; Column 7, 1-67; Column 8, lines 1-17].

6. The disclosure of this Blecha *et al.* patent references also explicitly states in detail what the direct teachings and implied suggestions of the described invention and the experimental tests and empirical results actually are: These are stated to be: (a) The COOH-terminus of the PR-39 structure does not contribute to antibacterial activity; (b) the N-terminus of the PR-39 structure is not sufficient for antibacterial activity; (c) the PR-26 truncated peptide containing residue Nos. 1-26 of the original PR-39 structure is the antibacterial domain; and (d) a particular secondary peptide structure conformation is required for both the PR-26 truncated analog peptide and the original PR-39 original peptide in order that antibacterial activity exists [Column 6, lines 48-57].

7. The Blecha *et al.* disclosure explicitly states that the one and only truncated analog peptide structure demonstrably functional for its intended purpose and goal is the PR-26 truncated analog peptide. Of all six truncated analog peptides synthsized and experimentally tested, only the PR-26 peptide analog is deemed suitable for the stated goal and purpose via its demonstrated antibacterial activity [Column 8, lines 8-17].

In sum, the Blecha *et al.* '993 patent reference is strikingly different and radically remote from applicants' claimed invention. The explicitly stated difference and distinctions include: (a) The absolute requirement that any truncated analog peptide structure derived from the original PR-39 peptide must demonstrate potent anti-microbial properties and effects; (b) No other set of characteristics, traits or properties other than a potent and effective antibacterial activity is of any value or is of interest for any purpose; (c) Of all the six truncated peptide analogs synthesized and experimentally evaluated, only one – the PR-26 analog having 26 amino acid residues - was found to be biologically active or operative for its intended goal and purpose, anti-microbial activity; and (d) No peptide structure less than 26 residues in length which is a truncated analog of the original PR-39 peptide is either biochemically active or useful.

C. The Lack Of Relevance For The Cited And Applied Prior Art References Of Record

1. As regards the factual basis presented by the Gallo et al '273 patent which the Examiner erroneously believes offers support for an inherency rejection, attention is directed to the written disclosure of the reference itself as exemplifying what the Examiner has employed wrongly and subjectively. These facts include the following points of information (1) The PR-39 amino acid sequence must be employed as a 39 amino acid residue sequence at a minimum in order for biological activity to be demonstrated. (2) The entire 39 amino acid sequence of PR-39 might be part of a larger sized molecule such as a fusion protein, or when

mobilized to an inert substrate or targeted using a specific ligand, as part of a longer length protein. (3) The entire PR-39 peptide (and any of its longer length products) are collectively identified as "synducins" – all of which require the ability to induce expression of syndecan-1 or syndecan-4 as the specific biological activity and mechanism of action described in the examples of the '273 patent. (4) The "synducin" characteristics and limited mechanism of action are solely for effecting the increased syndecan-1 and syndecan-4 expression on the surface of only mesenchymal cells; no type of cell other an a mesenchymal cell responds the effect of PR-39. (5) The specific inducement of syndecan-1 and syndecan-4 mRNA within mesenchymal cells along is solely for purposes of causing an increase in the quantity of cell surface heparan sulfate. (6) The biochemically active PR-39 peptide compositions must include a specific and lengthy amino acid residue sequence which is Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid.

Moreover, the entire manner and means of use of the PR-39 peptide for any and all purposes is stated and explicitly limited within the '273 patent; and demands that the inducement of syndecans on the cell surface be a requisite outcome and consequence of the mechanism of action in each and every usage, clinically or otherwise. Thus, any series of manipulative steps which employs and relies on the information disclosed by this '273 patent reference must follow and incorporate all the severe restrictions as stated explicitly by this reference in order for any utility or result to be expected or foreseen.

Equally important are the explicit limits of the method and compositions employed by this '273 patent. The use of the PR-39 peptides fails to be active with a variety of non-mesenchymal cells, as experimentally proven; and the '273 patent reveals that if the targeted cells are not mesenchymal cells as such, no functional response or biochemical activity will

result or can be expected. In sum, all of the information disclosed or suggested by the '273 Gallo et al. patent is self-limiting and restrictive in its uses and applications.

The Examiner has also utilized this '273 patent reference with regard to the composition claims recited by pending claims 11-15 herein. Applicants note that this prior art reference teaches away from the very characteristics, properties and utilities demonstrated by applicants' defined invention. Applicants note in particular that the peptide compositions defined by presently pending claims 11-15 are all far shorter in length than the minimum 39 amino acid residue compositions of the '273 patent; are not a part of a fusion peptide or linked with any other molecule; and do not comprise or contain the requisite amino acid sequences which are explicitly required by the disclosure of the '273 patent reference. Thus, the Examiner has no basis at all for suggesting or believing that any shorter length peptide sequence – particularly those of 15, of 11 or 8 residue length – could be or would be biologically active or functionally useful for any purpose.

2. As regards the Blecha *et al.* '993 patent, which the Examiner also erroneously believes provides support for an inherency rejection, attention is directed to the facts disclosed by the patent itself as exemplifying what the Examiner has unfortunately chosen to overlook and ignore. This '993 disclosure includes such essential facts as: (1) The sole criteria of use for the described truncated peptide analogs is exclusively as anti-microbial agents. No other activity, property, or characteristic is revealed or suggested. (2) Only one synthesized truncated peptide analog of 26 amino acid residue length was empirically found to be biochemically active for its intended purpose. All other the synthesized truncated peptide analogs shorter than 26 residues in length had no anti-microbial activity and thus had no

utility as such. (3) The presence of an antibacterial domain as a distinct entity is required in order for the requisite antibacterial activity to exist within the truncated peptide analog; and only the original PR-39 peptide and the truncated PR-26 peptide analog encompassed the requisite antibacterial domain within their structures. (4) The mechanism for biological activity is specified and required in order that the 26 residue length peptide analog structure be functional for its intended purpose. Thus, the specified means and limited manner of interaction for the peptide analog having the requisite antibacterial domain is an essential part of the truncated peptide analog structure; and any peptide sequence of any length which is devoid of the required antibacterial domain cannot and is not functional or useful for the stated purpose and goal of killing microbes and inhibiting microbial growth and infections.

These are explicit, direct and unrelenting requirements for the Blecha *et al.* truncated peptide analogs as well as for the limited utility and function recognized for the PR-26 analog peptide. Thus, the Examiner has clearly failed to recognize that there is no information and no factual suggestion whatsoever for using the any truncated peptide analog for any purpose except as an antimicrobial agent. The entire mechanism of action described and the whole of the Blecha *et al.* disclosure is specified and compulsory for a peptide analog capable of antibacterial inhibition and antimicrobial killing capability, as stated by the description within this reference.

Applicants therefore affirm and maintain that the '993 patent reference of record does not teach and could not suggest to those of ordinary skill in the art that they should carry out the claimed process defined by claims 1-10 or employ the oligopeptide compositions defined by claims 11-15. Moreover, the '993 patent reference of record has also revealed that, even if the ordinary practitioner had thought of making or practicing applicants' claimed invention,

those of ordinary skill in this field would not have any reasonable expectation of success. Applicants further maintain and submit that there is nothing inherent or intrinsic in the cited and applied '993 patent of record which offers or provides a basis for any expectation which would render the subject matter of independent claims 1-14 respectively as being either implied or obvious. Accordingly, applicants' subject matter as a whole defined by claims 1-15 is a methodology and family of compositions which are novel and have substantial patentable merit.

For all reasons stated herein, applicants respectfully submit that multiple errors of fact and law have been made by the Examiner; and that, accordingly, independent claims 1, 2, and 11 are therefore allowable as presently defined.

Claims 3-10 and 12-14 depend from independent claims 1-2, 11 or 15; and merely provide particular limitations and preferred embodiments to the unique and non-obvious invention defined therein. Since independent claims 1-2, 11, and 15 are believed to be in condition for allowance and claims 3-10 and 12-14 respectively depend there from, these dependent claims are also believed to be allowable.

In view of the above discussion and detailed analysis of the many factual and legal errors presented by the Examiner, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiner is invited to call applicants' undersigned attorney should she feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Michael Simons & Youhe Gao
SERIAL NO.	:	09/276,868
FILED	:	March 26, 1999
FOR		"METHOD FOR PR-39 PEPTIDE REGULATED STIMULATION OF ANGIOGENESIS"
EXAMINER	:	F.T. Moezie
GROUP ART UNIT	:	1653
ATTORNEY'S DOCKET NO.	:	BIS-043

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commission for Patents, Washington, D.C. 20231 on: July 19, 2001

Attorney for applicants: David Prasliker

Signature: [signature]

Date: July 19, 2001

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MARKED UP VERSION OF AMENDED CLAIMS SUBMITTED
PURSUANT TO 37 C.F.R.1.121

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants, in fulfillment of and in accordance with the requirements of 37 C.R.F. 121 (b) (iii), hereby submit a marked up version of presently amended claims 1-2, 6, and 11-15 as follows:

1 (Twice Amended). A method for stimulating angiogenesis within a targeted collection of viable cells in-situ, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target for stimulation of angiogenesis;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using said effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) [at least] the α7 subunit of at least some of the proteasomes interact with said PR-39 oligopeptide collective member, and

(b) [at least a part of] the proteolytic degradation of at least one identifiable peptide [activity] mediated by said proteasomes with an interacting α7 subunit becomes [functionally altered] markedly inhibited while the proteolytic degradation mediated by said proteasomes with an interacting α7 subunit against other individual peptides remains unaltered, and

(c) the markedly inhibited [functionally altered] proteolytic degradation activity of said [the] proteasomes with said interacting α7 subunit results in a stimulation of angiogenesis in-situ.

2 (Twice Amended). A method for altering [a discriminating inhibition of] proteasome-mediated degradation of peptides in-site within a collection of viable cells, said method comprising the steps of:

identifying a collection of cells comprising viable cells in-situ as a target;

providing means for effecting an introduction of at least one member selected from the group consisting of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells;

introducing at least one member of the PR-39 oligopeptide collective to the cytoplasm of said targeted collection of cells using effecting means;

allowing said introduced PR-39 oligopeptide collective member to interact with such proteasomes as are present within the cytoplasm of said targeted collection of cells whereby

(a) [at least] the α7 subunit of at least some of the proteasomes interacts with the PR-39 oligopeptide collective member, and

(b) [at least a part of] the proteolytic degradation of at least one identifiable peptide [activity] mediated by said proteasomes with an interacting α7 subunit becomes [functionally altered] markedly inhibited while the proteolytic degradation mediated by said proteasomes with an interacting α7 subunit against other individual peptides remains unaltered, and

(c) the markedly inhibited [functionally altered] proteolytic degradation [activity] of the proteasomes with said interacting α7 subunit results in a an increased expression of said identifiable peptide in-situ within the targeted collection of cells [discriminating inhibition of proteasome-mediated degradation for at least one specific peptide in-situ].

6 (Twice Amended). The method as recited in claim 1 or 2 wherein the means for an introduction of a PR-39 oligopeptide collective member includes DNA sequences coding for at least one PR-39 oligopeptide collective member in an vector suitable for transfection and subsequent expression of the PR-39 within said cells.

11 (Twice Amended). A family of PR-39 derived oligopeptides whose member[are biochemically active and individually] cause an [a functional] inhibition of proteasome-mediated degradation for at least one identifiable [specific] peptide in-situ after introduction intracellularly to a viable cell, each member of said oligopeptide family being:

[a peptide substantially] less than 26 [39] amino acid residues in length;

an oligopeptide [a peptide] whose N-terminal amino acid residue sequence which begins with Arg-Arg-Arg;

at least partially homologous with the [N-terminal] amino acid sequence of native PR-39 peptide;

pharmacologically active for markedly altering the proteolytic degradation activity of proteasomes in-situ;

able to interact in-situ with a least the α7 subunit of such proteasomes as are present within the cytoplasm of the cell; and

able to alter the [functional] proteolytic degradation activity of said proteasomes having an interacting α7 subunit such that the proteolytic degradation mediated by said proteasomes against at least one identifiable peptide becomes markedly inhibited while the proteolytic degradation mediated by said proteasomes against other individual peptides

remains unaltered [a markedly increased expression of at least one specific peptide occurs in-situ].

12 (Twice amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 15 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr-Leu-Pro-Arg-Pro-Arg-Pro-Pro [SEQ ID NO: 3].

13 (Twice amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 11 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr-Leu-Pro-Arg [SEQ ID NO: 4].

14 (Twice amended). The PR-39 derived oligopeptide family as recited in claim 11 or 15 whose membership includes a peptide comprised of 8 amino acid residues whose sequence is Arg-Arg-Arg-Pro-Arg-Pro-Pro-Tyr [SEQ ID NO: 5].

15 (Once amended). A family of PR-39 derived oligopeptides whose members [are biochemically active and individually] cause an [a functional] inhibition of protease-mediated degradation of at least one identifiable [specific] peptide in-site after introduction intracellularly to a viable cell, each member of said oligopeptide family being:

[a peptide] less than 20 amino acid residues in length;

an oligopeptide [a peptide] whose N-terminal amino acid residue sequences begins with Arg-Arg-Arg;

at least partially homologous with the [N-terminal] amino acid sequence of native PR-39 peptide;

pharmacologically active for markedly altering the proteolytic degradation activity of proteasomes in-situ;

able to interact in-situ with at least the α7 subunit of such proteasomes as are present within the cytoplasm of the cell; and

able to alter the [functional] proteolytic degradation activity of said proteasomes having an interacting α7 subunit such that the proteolytic degradation mediated by said proteasomes against at least one identifiable peptide becomes markedly inhibited while the proteolytic degradation mediated by said proteasomes against other individual peptides remains unaltered [a markedly increased expression of at least one specific peptide occurs in-situ].

Respectfully submitted.

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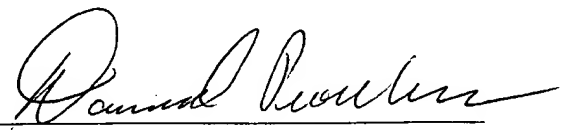
By: 

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